Accepted Manuscript

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PII: S0141-8130(18)33118-0
DOI: doi:10.1016/j.ijbiomac.2018.09.102
Reference: BIOMAC 10537

To appear in: *International Journal of Biological Macromolecules*

Received date: 23 June 2018
Revised date: 27 August 2018
Accepted date: 17 September 2018

Please cite this article as: Saikat Pal, Sandip Paul , Conformational Deviation of Thrombin Binding G-quadruplex Aptamer (TBA) in Presence of Divalent Cation Sr2+: A Classical Molecular Dynamics Simulation Study. Biomac (2018), doi:10.1016/j.ijbiomac.2018.09.102

Available online at www.sciencedirect.com

ScienceDirect

International Journal of Biological Macromolecules 00 (2018) 1–??

Int. J. Biol. Macromol.

www.elsevier.com/locate/procedia

Conformational Deviation of Thrombin Binding G-quadruplex Aptamer (TBA) in Presence of Divalent Cation Sr^{2+}: A Classical Molecular Dynamics Simulation Study

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Abstract

Thrombin binding TBA-G-quadruplex aptamer (TBA) plays a major role in blood coagulation cascade. The 15-mer TBA sequence tends to form four-stranded TBA-G-quadruplex structure. In this research work, a series of explicit solvent classical MD simulations of the TBA is carried out using different salt ($SrCl_2$) concentrations (0, 50, 100 and 200 mM). Here we have also testified the effect of salt concentration of divalent cation Sr^{2+} on the conformational change of quadruplex DNA. The structural deviations, fluctuations, torsional angles and the affinity of the ion are explored at different salt concentrations. It is found that the conformation of TBA-G-quadruplex at 0 mM and 50 mM salt concentrations, are very much different than the other salt concentrations (100 mM and 200 mM). Also observed are: (i) no exchange of Sr^{2+} ion between inside and outside of the channel, (ii) an enhancement in the Sr^{2+} ion density around the phosphate region of the loop residues as salt concentration increases and (iii) the stacking of T3 and T4 residues of loop-1 that appears up to 50 mM concentration, vanishes as the salt concentration is increased further.

Keywords: G-quadruplex, Divalent cation (Strontium), Molecular dynamics, Thrombin binding Aptamer.

1. Introduction

DNA, a polymeric unit of nucleotides in living cells, is involved in transmitting, encoding and expressing genetic information. It can adopt different confirmations based on its sequence and physiologically relevant conditions[1]. DNA is most commonly present as double helical B-DNA, but it can also form various hairpins, triplexes, motifs, quadruplex and hybrid structures. Among these structures, non-canonical quadruplex nucleic acids [2, 3, 4, 5, 6, 7, 8, 9] have the potential to form into the four-stranded helical structure using four guanines hoogsteen-paired hydrogen bonded to each other and π-π stacking of quartet of guanines.

G-quadruplex molecules have been also found to communicate with different proteins like α-thrombin [10, 11, 12, 13] , nucleolin [14, 15, 16], STAT3 protein [17, 18, 19]. Malfunctioning of α-thrombin causes hemorrhage and thrombosis, which further leads to coronary heart disease and thrombotic disorders. Therefore, to affect the action of the α-thrombin, there is a need for a specific inhibitor. In 1992, Bock et al. found that the 15-mer quadruplex DNA acts as an inhibitor of thrombin, called a Thrombin Binding Aptamer

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